5. Thoman ME, Verhulst HL: Ipecac syrup in antiemetic ingestion. JAMA 196:433-434, 1966
6. Bourianoff G: No time for ipecac. Emergency Med 3:5, 1971
7. MacLeod J: Ipecac intoxication—Use of a cardiac pacemaker in management. N Engl J Med 268:146-147, 1963
8. Diamant EJ: Carbohydrate metabolism in emetine-poisoned rats. J Pharmacol Exp Ther 122:465-473, 1958
9. Bates T, Grunwaldt E: Ipecac poisoning. Am J Dis Child 103:169-173, 1962
10. Goodman L, Gilman A (Eds): The Pharmacologic Basis of Therapeutics, 5th Ed. New York, Macmillan, 1975, p 1076
11. Allport RB: Ipecac is not innocuous. Am J Dis Child 98: 786-787, 1959
12. Speer JD, Robertson WO, Schultz LR: Ipecacuanha poisoning another fatal case. Lancet 1:475-477, 1963
13. Smith RP, Smith DM: Acute ipecac poisoning. N Engl J Med 265:523-525, 1961
14. Rose NJ: Report of accidental poisoning death from fluid extract of ipecac. Ill Med J 137:338, 1970
15. Manno B, Manno J: Toxicology of ipecac. Clin Toxicol 10:221-242, 1977

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Legionnaires Disease Causing Adult Respiratory Distress Syndrome

Survival and Report of Open Lung Biopsy

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LEGIONNAIRES DISEASE may result in a fulminant pneumonia. This disease occurs in both epidemic and sporadic cases. No doubt this entity is more common than was previously recognized. We successfully treated a patient in whom adult respiratory distress syndrome developed secondary to Legionnaires disease. The purpose of this report is to detail the clinical features of this case and review an open lung biopsy study done four days after hospital admission. We are not aware of previous lung biopsies done in cases of this disease. The biopsy study showed pronounced leukocytic infiltration, edema fluid and hyaline membranes. Legionnaires disease should be considered in differential diagnosis of adult respiratory distress syndrome especially if there are leukocytic histologic features.

Hyponatremia present on admission was due to inappropriate secretion of antidiuretic hormone.

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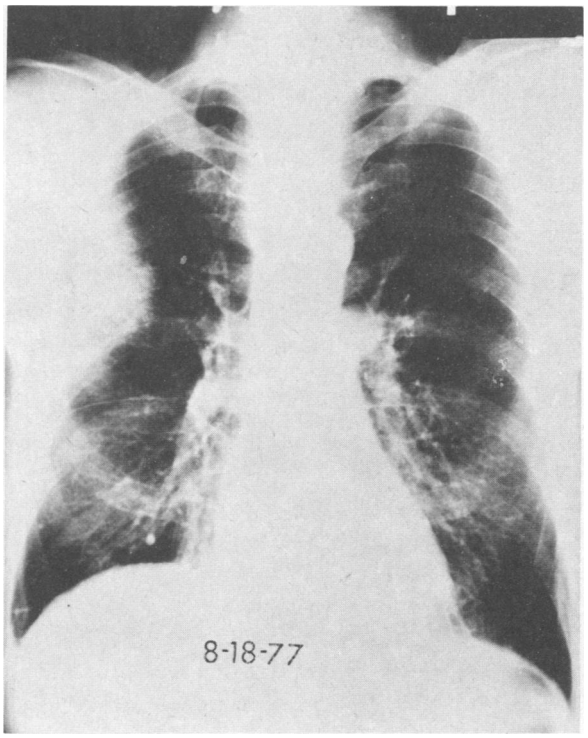

Figure 1.—X-ray film of the chest made on admission showing right upper lobe pneumonia.

Pulmonary function tests following discharge returned to normal. A mild relapse occurred one week following discharge.

Report of a Case

A 58-year-old white man was admitted to Samuel Merritt Hospital, Oakland, with a chief complaint of high fever. He had been in his usual state of health until three days before admission, when malaise began. Two days before admission, nausea and retching occurred. On the morning of admission his temperature was 40°C (104°F) and an x-ray study of the chest (Figure 1) showed wedge-shaped alveolar infiltrate in the right upper lobe. The patient had noted no respiratory symptoms; specifically no cough, sputum production, chest pain, dyspnea, wheezing, sore throat or coryza. He said that diarrhea, frequency or dysuria had not been present.

A diagnosis of multiple sclerosis had been made 25 years earlier but this condition had never caused any significant problems. He had smoked one pack of cigarettes per day for the past 40 years.

On physical examination at admission, blood pressure was 140/80 mm of mercury; pulse, 92 per minute; respirations, 18 per minute, and

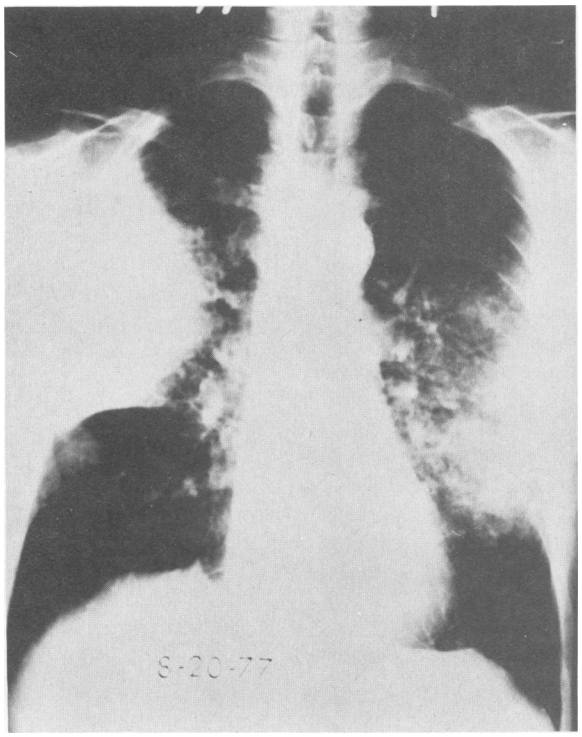

Figure 2.—X-ray film of the chest made on the third day showing progression of pneumonia on right and spread to left middle and lower lung fields.

temperature, 40.3°C (104.6°F). There were a few rales in the right chest. There were no other positive findings.

Initial laboratory studies gave the following values: hemoglobin, 13.1 grams per dl; leukocyte count, 11,000 with 91 percent neutrophils, 5 percent lymphocytes, 4 percent monocytes; sodium, 124 mEq per liter; potassium, 4.2 mEq per liter; blood urea nitrogen, 12 mg per dl; creatinine, 0.9 mg per dl; serum glutamicoxalacetic transaminase, 53 U (upper limit of normal, 35 U). Arterial blood gas studies, on room air showed a pH of 7.51, a carbon dioxide pressure (Pco_2) of 24 mm of mercury, and an oxygen pressure (Po_2) of 65 mm of mercury. Findings on analysis of urine were unremarkable. Initial sputum Gram stain showed only rare leukocytes and no organisms. Culture subsequently grew no pathogens.

Hospital Course

The admitting diagnosis was viral pneumonia. However, after all the cultures were obtained treatment was instituted with 1 million units of penicillin given intravenously every six hours. The serum osmolality was 215 mOsm per liter, with urine sodium of 27 mEq per liter. A simultaneous urine osmolality was 680 mOsm per liter which confirmed the diagnosis of inappropriate antidiuretic hormone secretion. The patient was treated with fluid restriction.

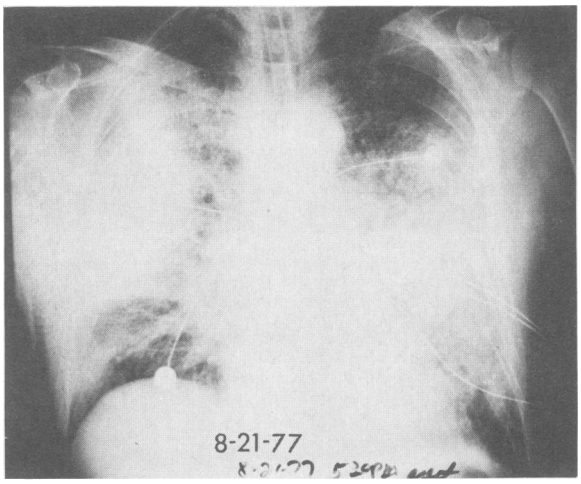

Figure 3.—Chest on fourth day showing "white out" of both lungs.

On the third day an x-ray film of the chest (Figure 2) showed increased infiltrate in the right upper lobe and a new infiltrate in the left lower lobe. Body temperature remained at 40°C (104°F). For the first time he complained of dyspnea. The penicillin was stopped and parenteral methicillin therapy (1 gram every six hours) and gentamycin administration (80 mg every eight hours) were started empirically. All cultures remained negative. Sputum production remained minimal and findings on Gram stain again were unremarkable. The leukocyte count was 7,800 with 52 segmented neutrophils and 44 bands. Skin tests for tuberculosis and coccidioidomycosis were negative. An antinuclear antibody study was negative.

On the fourth hospital day, x-ray films of the chest showed both lung fields were opacified (Figure 3); and the patient was in pronounced respiratory distress. Intubation was carried out and assisted ventilation begun. Arterial blood gas studies on inspired oxygen concentration of 100 percent showed a pH of 7.41, Pco_2 of 25 mm of mercury, and Po_2 of 150 mm of mercury. Later that evening he became hypotensive and a dopamine drip was started. A Swan-Ganz catheter was inserted and the pressures were as follows: right ventricle, 30/0 mm of mercury, pulmonary artery, 30/12 mm of mercury with a mean of 19 mm of mercury; pulmonary artery wedge, 10 mm of mercury. Treatment was carried out with an in-

fusion of salt poor albumin, furosemide (Lasex®), digitalis and 1 gram of methylprednisolone. Positive and expiratory pressure (PEEP) was added. However, the alveolar-arterial oxygen gradient continued to widen.

On the morning of the fifth hospital day, blood gas studies showed a pH of 7.44, P_{CO_2} of 20 mm of mercury and P_{O_2} of 55 mm of mercury on inspired oxygen concentration of 100 percent and PEEP of 15 cm of water. This further deterioration occurred despite the fact the wedge pressure remained below 10 mm of mercury at all times. However, the patient's blood pressure stabilized and dopamine administration was discontinued.

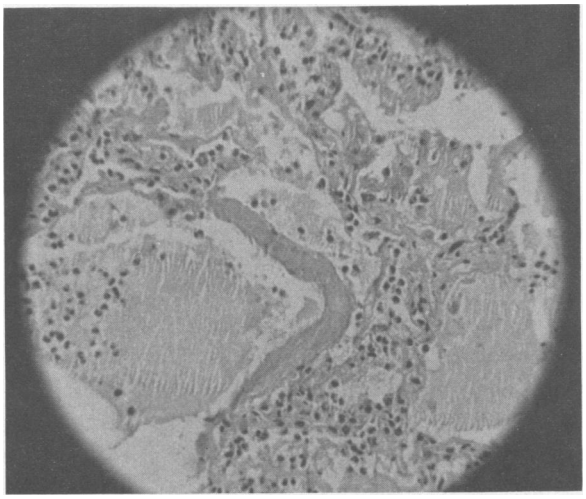

Figure 4.—Microscopic section showing hyaline membrane, (in center of field) edema fluid and polymorphonuclear leukocytes. (H & E stain, reduced from ×200)

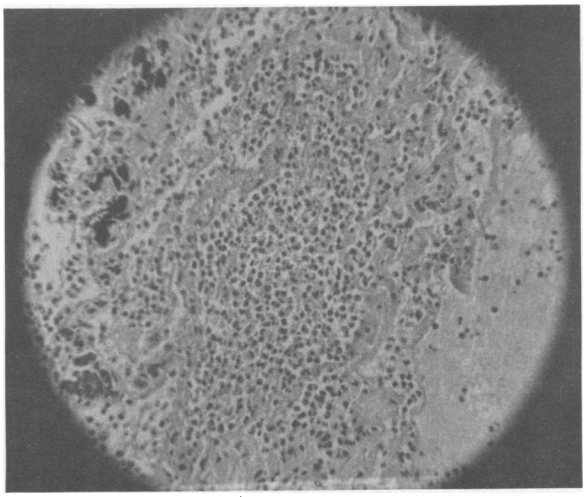

Figure 5.—Microscopic section showing pronounced polymorphonuclear leukocyte infiltration. (H & E stain, reduced from ×200)

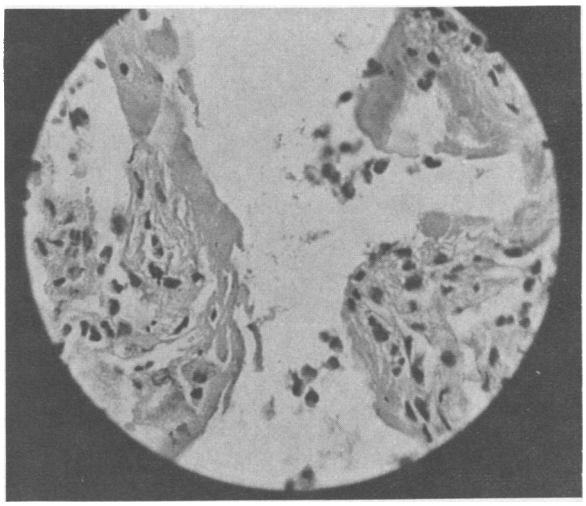

Figure 6.—Microscopic section showing prominent hyaline membranes. (H & E stain, reduced from ×800)

Because the cause of this rapidly progressive pneumonia remained uncertain, an open lung biopsy study was done on the fifth day. This was less than 24 hours after intubation and exposure to high concentrations of inspired oxygen. Study of the lung biopsy specimen (Figures 4-6) showed pronounced polymorphonuclear (PMN) leukocyte infiltration within the alveoli and alveolar septa. There were eosinophilic hyaline membranes present. Some alveoli contained pink, protein-rich edema fluid. There were no granulomas, nuclear inclusions or vasculitis seen. There was no squamous metaplasia or ulceration of the bronchial mucosa. Gram stain showed no organisms. Because of the possibility of Legionnaires disease, erythromycin, 250 mg every six hours, was added to the antibiotic regimen.

On the evening of the fifth day, the first decline in the patient's alveolar-arterial oxygen gradient occurred. Subsequently, slow steady improvement began. Administration of antibiotics was stopped on the 12th day. On the 15th day PEEP was discontinued. By the 21st day mechanical ventilation was no longer required. On the 24th day he became afebrile for the first time and remained so until discharge. Arterial blood gas studies on room air showed a pH of 7.43, a P_{CO_2} of 34 mm of mercury and a P_{O_2} of 70 mm of mercury. The hemoglobin was 11.4 grams per dl; hematocrit, 32 percent; leukocyte count, 11,700 with 69 segmented neutrophils and 6 bands. The sodium value was 135 mEq per liter. Improvement continued to be seen on x-ray studies and

there remained only mild streaking at the left base. He was discharged after 30 days in hospital.

After Discharge

A week following discharge of the patient the Center for Disease Control confirmed the diagnosis of Legionnaires disease. By means of an indirect fluorescent antibody technique the patient's serum was tested against two isolates of the Legionnaires bacterium. The serum taken during the acute phase showed titers of less than 32. The serum taken during convalescence showed a titer of 128 to one of the isolates and showed a titer of 256 to the other isolate. These titers are diagnostic of recent infection with the Legionnaires bacterium. Other serologic studies, including those for plague, tularemia, mycoplasma, Q fever, toxoplasmosis, psittacosis, cytomegalovirus, influenza and adenovirus, were negative.

After the patient had been home for one week, elevations in body temperature occurred to nearly 39°C (101° to 102°F). There was no cough, sputum production, dysuria or diarrhea. The fevers persisted and a 14-day course of erythromycin was instituted. After four days of therapy with erythromycin, the patient's body temperature returned to normal and remained so subsequently. Pulmonary function testing showed that spirometry and lung volumes were within normal range. The patient's condition has continued to improve and he is doing quite well approximately one month after his discharge.

Comment

Legionnaires disease is the name that has been applied to the acute illness that afflicted some 180 people who attended an American Legion convention in Philadelphia in 1976. The cause of the disease was not initially apparent. After much investigative work the etiologic agent was found.[1-3] The reasons for difficulty in discovering the agent were (1) the organism is difficult to culture on standard bacteriologic media and (2) the organism does not stain in tissue sections with usual stains.

Lung tissue obtained postmortem from several patients was inoculated into guinea pigs. These animals became ill and were killed. Portions of spleen, liver and lungs were inoculated into embryonated hens' eggs. The eggs died, and smears of the yolk sac stained by the Gimenez method showed bacilli. Gram stain showed the organism to be a Gram negative rod. The acute and convalescent sera from patients with Legionnaires disease were incubated with this organism, and by means of an indirect fluorescent antibody technique significant rises in titers were shown.

The bacterium is slow growing and difficult to culture. It has been isolated on bacteriologic medium in rare instances from lung tissue and pleural fluid. It has not been isolated from sputum, transtracheal aspiration or bronchial washings. The Center for Disease Control recommends that attempts to grow the organism should be done with Mueller-Hinton agar with hemoglobin and Isovitalex®. In tissue sections the organism stains poorly with Gram stain and Giemsa stain. It does not stain at all with hematoxylin and eosin, acid fast or methenamine silver. The organism can be shown to be present in tissue by means of the dieterle silver impregnation procedure. Most cases are diagnosed by serologic means using an indirect fluorescent antibody technique.

With the advent of this test, it is evident Legionnaires disease is neither localized nor new. The same bacterium caused outbreaks of pneumonia in Washington, DC, in 1965; Pontiac, Michigan, in 1968, and Philadelphia in 1974. Since August 1976 more than 20 sporadic cases have been identified from 11 states. Our case is the first to be documented in the San Francisco Bay area and the fifth in California. The patient did not leave the Bay area in the several months before his illness and undoubtedly contracted the disease here.

In the typical case seen in the Philadelphia outbreak, the earliest symptoms were malaise, myalgia and headache. These were associated with fever which was usually quite high—38.8° to 40.5°C (102 to 105°F)—and a nonproductive cough. Gastrointestinal complaints developed in many patients. When first examined, most patients had rales but no evidence of consolidation. The remainder of the physical examination usually gave normal findings. Leukocytosis with left shift and proteinuria were frequently seen. Less commonly, hyponatremia, mild azotemia, elevated serum glutamic oxalacetic transaminase, or elevated alkaline phosphatase were present. X-ray studies of the chest showed patchy interstitial infiltrates or areas of consolidation which tended to progress. In more seriously afflicted persons the clinical condition usually deteriorated over the next two to three days following hospital

admission. Death from shock or respiratory failure resulted in a mortality rate of approximately 15 percent. Gastrointestinal bleeding was not uncommon. In several patients, acute renal failure was seen. There were no secondary cases noted among either family members or medical staff who cared for the patients. The exact mode of transmission of the disease is uncertain. It is probably acquired by inhalation. It would appear doubtful that it is transmitted from person to person.

Our patient was ill for three days before being admitted to hospital. Surprisingly, he had no respiratory complaints. There was no cough, sputum production or chest pain on admission even though an x-ray film showed right upper lobe pneumonia. Once the patient was admitted to hospital, there was frighteningly rapid progression of the pneumonia. By the fourth hospital day, both lung fields were completely opacified and assisted ventilation was required. The difficulty with oxygenation was severe. At the nadir, the arterial P_{O_2} was only 55 mm of mercury on inspired oxygen concentration of 100 percent and PEEP of 15 cm of water. This difficulty cannot be ascribed to fluid overload as wedge pressure never exceeded 10 mm of mercury, nor to decreased oncotic pressure as serum albumin remained in normal range. The patient was treated with standard measures for adult respiratory distress syndrome.[4,5] His response was slow but gradual. He remained on PEEP for ten days and assisted ventilation was required for 16 days.

An open lung biopsy study was done less than 24 hours after he was placed on a ventilator and exposed to high oxygen concentrations. The biopsy specimen was characterized by pronounced infiltration with polymorphonuclear leukocytes and the changes consistent with acute alveolar injury. There was a great amount of protein-rich edema fluid and evidence of hyaline membranes. Areas of intra-alveolar hemorrhage were seen. It usually takes several days of exposure to high oxygen concentrations for hyaline membranes and other changes of acute alveolar injury to develop.[6] Their presence on the biopsy specimen obtained so soon after intubation and exposure to high oxygen concentrations would suggest that the major factor producing the pattern of acute alveolar injury was the Legionnaires bacterium.

In a patient with pneumonia in whom no bacterial pathogens have been cultured, the presence of pronounced polymorphonuclear leukocyte infiltration on a lung biopsy specimen should raise strong suspicion of Legionnaires disease. At present, the dieterle silver stain which shows the presence of the organism is not widely available.

TABLE 1.—*Pulmonary Function Test Results*

	Predicted	*1972*	*1977*
Forced vital capacity (liters)	4.6	5.0	4.7
Forced expiratory volume in one second (liters)	3.5	3.9	3.9
Maximum midexpiratory flow (liters per second)	4.7	3.9	4.1
Total lung capacity (liters)	7.0	7.4	6.7
Residual volume (liters)	2.4	2.4	2.1

There have been no randomized trials of antibiotic efficacy in humans. *In vitro* studies have suggested that the organism is sensitive to a number of antibiotics including erythromycin, a number of the penicillins, cephalosporins, the aminoglycosides and chloramphenicol. Erythromycin has been effective against experimental infections in guinea pigs. A case report from the Mayo Clinic suggested that tetracycline was effective.[7]

In our case no statement can be made regarding the relative efficacy of the antibiotics received: methicillin, gentamycin and erythromycin. There was no great change in the clinical course following the institution of any of these agents. The patient remained febrile for more than three weeks and the fever subsided 12 days after all antibiotics had been stopped. Because a definitive diagnosis was lacking while the patient was in hospital, he may not have received optimum antibiotic therapy. The recurrence of fever after discharge suggests that relapse or incomplete irradication of the organism may occur. This fever responded to the reinstitution of erythromycin therapy. One might speculate that patients who are severely ill from Legionnaires disease may require several weeks of treatment with erythromycin or other antibiotics to prevent such recurrences and to hasten recovery.

Several recent papers have reported the pulmonary function status in patients who survived adult respiratory distress syndrome from diverse causes.[8,9] They found no evidence of significant impairment of function. The pulmonary function status of our patient has not changed significantly from that of five years ago (Table 1). An x-ray film of the chest has shown complete clearing (Figure 7). Therefore, Legionnaires disease caus-

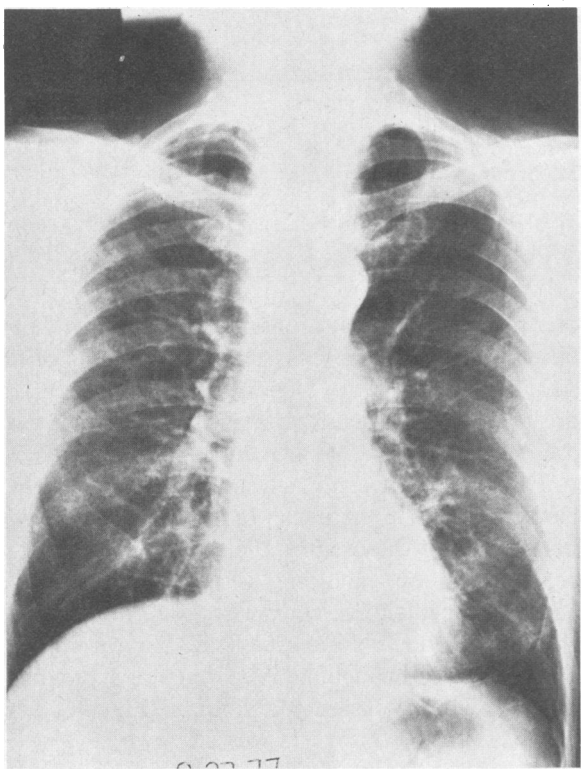

Figure 7.—X-ray film of the chest taken ten days after discharge showing complete clearing of the infiltrate.

ing acute respiratory failure does not appear to result in significant permanent pulmonary damage if the patient survives.

The characteristic features of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) include (1) hyponatremia associated with hypoosmolality of serum, (2) urine which is not maximally dilute in face of serum hypoosmolality, (3) continued urinary excretion of sodium despite hypoatremia, (4) normal renal and adrenal function, (5) absence of hypotension, dehydration or azotemia, (6) absence of edema and (7) correction following fluid restriction. On admission to hospital our patient fulfilled these criteria.

There have been several isolated reports of SIADH occurring with bacterial and viral pneumonia.[10,13] The frequency is uncertain, but it does not appear to be high. Fever is one of the known nonosmotic stimuli for release of antidiuretic hormone. Since Legionnaires disease frequently is accompanied by high fevers, the association of this particular pneumonia with SIADH may be more common.

Summary

An isolated case of Legionnaires disease causing adult respiratory distress syndrome was seen in the San Francisco Bay area. This entity should be considered in differential diagnosis of any severe pneumonia. An open lung biopsy study showed pronounced polymorphonuclear leukocyte infiltration, edema fluid and hyaline membranes. Following discharge of the patient there was recurrence of fever, suggesting that relapse may occur. There does not appear to be any significant permanent pulmonary damage if the patient can survive the acute episode. Finally, Legionnaires disease can be associated with the syndrome of inappropriate secretion of antidiuretic hormone.

REFERENCES

1. Fraser DW, Tsai TF, Onenstein W, et al: Legionnaires' disease: Description of an epidemic of pneumonia. N Engl J Med 297:1189-1197, 1977

2. McDade JE, Shepard CC, Fraser DW, et al: Legionnaires' disease: Isolation of a bacterium. N Engl J Med 297:1197-1203, 1977

3. Chandler FW, Hichlin MD, Blackmon JA: Legionaires' disease: Demonstration of the agent in tissue. N Engl J Med 297: 1218-1219, 1977

4. Petty TL, Ashbaugh DG: Adult respiratory distress syndrome—Clinical features, factors influencing prognosis and principles of management. Chest 60:233-239, 1971

5. Blaisdell WF, Schlobohm RM: Respiratory distress syndrome: A review. Surgery 74:251-262, 1973

6. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368-374, 1967

7. Keys TF: Sporadic case of pneumonia due to Legionnaires' disease. Mayo Clin Proc 52:657-660, 1977

8. Rotman HH, Lavelle TF, Demcheff DG, et al: Long-term physiologic consequences of the adult respiratory distress syndrome. Chest 72:190-192, 1977

9. Douglas ME, Downs JB: Pulmonary function following severe acute respiratory failure and high levels of positive end-expiratory pressure. Chest 71:18-23, 1977

10. Stormont JM, Waterhouse C: Severe hyponatremia associated with pneumonia. Metabolism 11:1181-1185, 1962

11. Rosenow EC III, Segar WE, Zehr JE: Inappropriate antidiuretic hormone secretion in pneumonia. Mayo Clin Proc 47: 169-174, Feb 1972

12. Bryant DH: Syndrome of inappropriate secretion of antidiuretic hormone in infectious pulmonary disease. Med J Aust 1: 1285-1288, 1972

13. Bollard RB: Inappropriate secretion of antidiuretic hormone associated with adenovirus pneumonia. Chest 68:589-591, 1975